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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,486	CIPOLLONE ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *11-13,16,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-10, 14-15 and 17 in the reply filed on 12/8/2008 is acknowledged. The traversal is on the ground(s) that the kit of invention II incorporates the same technical feature (i.e., the detection of a mutation at position 436 of SEQ ID NO: 1. Applicant states that Stanton et al does not disclose this limitation. Applicant summarizes the instant invention and states that the prior art does not disclose the special technical feature common to Group I and II, which is detection of the mutation at position -765 of the Cox-2 promoter. The arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow. In response to Applicant's arguments that the kit of claim 11 incorporates the same technical feature as the method of claim 1, the Examiner respectfully disagree because the limitation "for carrying out the method according to claim 1" is non-limiting and is an intended use of the claimed "kit" that does not carry any patentable weight. The claim 11 of Group II as broadly written only requires that a "kit", which is a compilation of reagents, be present. Contrary, to Applicant's arguments, the kit is not limited to any specific structure, mutation, or method steps. The kit cannot perform any specific method steps or yield any specific product. Thus, the Examiner maintains that the inventions of Groups I and II are not related to a single general inventive concept and thus lack the same or corresponding technical feature. The requirement is still deemed proper and is therefore made FINAL. Accordingly, the claims 11-13, 16, 18 and 19 are withdrawn from consideration as being drawn to a non-elected invention.

Specification

2. The disclosure is objected to because of the following informalities:

(a) The disclosure is objected at pages 2-4, 8-10 and because the designation for the sequence identifier is improper (see MPEP§ 2422.03). It is suggested amending the disclosure to recite --SEQ ID NO:--.

Appropriate correction is required.

Claim Objections

Claims 1, 8 and 9 are objected to because of the following informalities:

(a) The claims 1, 8 and 9 are objected because the designation for the sequence identifier is improper (see MPEP§ 2422.03). It is suggested amending the disclosure to recite --SEQ ID NO:--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for assessing in vitro the predisposition of a subject to develop cardiovascular diseases comprising several method steps... wherein the presence of a cytosine at nucleotide position 436 of SEQ ID NO:1 in at least one DNA allele of a subject indicates a lower risk for predisposition to

cardiovascular diseases than the presence of guanosine at nucleotide position 436 of SEQ ID NO: 1 on both alleles *or* while being enabling for a prognostic method for a cardiovascular pathology comprising several method steps...wherein the presence of a cytosine at position 436 of SEQ ID NO: 1, in at least one DNA allele of a subject indicates a low sensitivity to therapy with non-steroidal anti-inflammatory drugs than the presence of a guanosine (G) in position 436 on both alleles, it does not reasonably provide enablement for a method for assessing in vitro the predisposition of a subject to develop cardiovascular pathologies comprising identifying any nucleotide corresponding to position 436 of SEQ ID NO: 1 on a sample of genomic DNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

The claimed invention is drawn to a method for assessing in vitro the predisposition of a subject to develop cardiovascular pathologies, comprising identifying the nucleotide corresponding to position 436 of SEQ ID NO: 1 on a sample of genomic DNA of said subject. The specification teaches at page 4, that the present invention is based on the clinical confirmation of the existence of a relationship between the C/G polymorphism in the COX-2 promoter in position corresponding to nucleotide 436 of SEQ ID NO: 1 and the instability of the atherosclerotic plaque. The specification teaches at page 4 that the method essentially comprises the identification of the nucleotide at position -765 corresponding to nucleotide 436 of SEQ ID NO: 1 from the transcription start site of the cyclooxygenase-2 gene on a sample of genomic DNA from a biological sample of such subject. In the specification at page 8 and 9 and in the Table 2, the specification discloses that the presence of a guanosine (G) at position -765 on both alleles in homozygous configuration of the COX-2 gene promoter of a subject correlates with an increase risk for predisposition to cardiovascular diseases as compared to the presence of cytosine at position -765 of the COX-2 gene promoter on at least one allele of DNA which indicates a lower risk for predisposition of cardiovascular diseases or a reduce sensitivity to the therapy with non steroidal anti-inflammatory drugs.

The specification however does not correlate the identification of any nucleotide at position with a predisposition to cardiovascular diseases. The specification does not provide any guidance as to how the method of assessing in vitro the predisposition of a subject to develop cardiovascular pathologies is to operate by identifying any

nucleotide, polymorphic change or mutation at position 436 of SEQ ID NO: 1 and associated it with any type of cardiovascular disease or any type of non-steroidal anti-inflammatory drugs. There are no working examples or data presented which supports any polymorphic change or mutation at position 436 of SEQ ID NO: 1 as effectively assessing any of the many forms of cardiovascular diseases and/or drug treatment. There are no working examples which disclose how one would go about correlating the detection of any nucleotide at 436 of SEQ ID NO: 1 with any type of risk to a predisposition to cardiovascular diseases or any type of treatment or therapy to a drug. The art supports the identification of a COX-2 promoter variant -765 G>C being associated with coronary artery disease (Papafili et al., Arterioscler Thomb Vasc Biol, vol. 22, pages 1631-1636, 2002, citation made of record on IDS). The art does not support any nucleotide change, polymorphism or variant being associated with any risk for cardiovascular disease. However, no art was found wherein any nucleotide change, any type of mutation or polymorphism is inherently related to cardiovascular diseases. Thus, it is unpredictable that any nucleotide change at position 436 of SEQ ID NO: 1 will result in assessing a subject's predisposition to any form of cardiovascular pathology or determine a subject's sensitivity to treatment with a non-steroidal anti-inflammatory drug. In view of the foregoing, further experimentation is deemed necessary to practice the invention as currently written commensurate fully in scope.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10, 14-15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims 1-10, 14-15 and 17 are indefinite in the claims 1, 14 and 15 for the limitation in parentheses "(COX-2 gene promoter)" because in cannot be determined whether the limitations within parentheses are intended to define the claim or is a separate entity. It is suggested amending the claims such that the parentheses are removed.

(b) The claims 1-10 are indefinite in the claim 1 because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a method of assessing in vitro the predisposition of a subject to develop cardiovascular pathologies. However, the claims only recite a single step of identifying the nucleotide corresponding to position 436 of SEQ ID NO: 1". Thus it cannot be determined if the goal of the preamble, i.e., for assessing in vitro disposition of a subject to develop cardiovascular pathologies, is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method of identifying a specific target nucleotide" or "a method of detecting SEQ ID NO: 1". While minute details are not required in method claims, at least the basic steps

must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986). Clarification is required as to Applicant's intent.

(c) The claim 8 is indefinite and confusing at the recitation of "at least partially identical" because the limitation has not been defined in the specification or claims and it cannot be determined how the limitation modifies the sequence of SEQ ID NO: 3 and 4. Clarification is required.

(c) Claims 14-15 and 17 are indefinite in the claim 14 because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a prognostic method for cardiovascular pathologies selected from the pathologies recited in the claim 14. However, the claims only recite a single step of genotyping of a nucleotide at position 436 of SEQ ID NO: 1". Thus it cannot be determined if the goal of the preamble, i.e., determining prognosis for a cardiovascular pathology, is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method genotyping.....". While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986). Clarification is required as to Applicant's intent.

Claim interpretation

The claim invention is drawn to a method for assessing in vitro the predisposition of a subject to develop cardiovascular pathologies, comprising identifying the nucleotide corresponding to position 436 of SEQ ID NO: 1 on a sample of genomic DNA of said subject. The claims 1, 14 and 15 as broadly written do not provide any steps which

suggest that the *single method step* of identifying or genotyping the nucleotide corresponding to position 436 of SEQ ID NO: 1 on a sample of genomic DNA of a subject results in assessing in vitro the predisposition of a subject to develop cardiovascular pathologies or any prognostic method to cardiovascular diseases or assessing the sensitivity to therapy with a non-steroidal anti-inflammatory drugs. Additionally, it cannot be determined how the limitation in parentheses of claim 1 limits or defines the instant claim. Thus, for the purpose of application of prior art, the claims 1 and 14 are being interpreted by the Examiner as "a method comprising the single step of identifying a nucleotide corresponding to position 436 of SEQ ID NO: 1 on a sample of genomic DNA of a subject". With regards to claim 15, the claim is being interpreted by the Examiner as "a method of genotyping of nucleotide at position 436 of SEQ ID NO: 1

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-7, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Papafili et al (Arteriosclerosis, Thrombosis, and Vascular Biology, published online before print on July 18, 2002, citation made of record on IDS filed 10/16/1996). Regarding claims 1, 14 and 15, Papifili et al teach a method comprising identifying or genotyping a nucleotide corresponding to nucleotide position -765 on a sample of

genomic DNA of a subject (page 1634, col. 2, lines 14-21). Papafili et al do not recite wherein that the nucleotide position is at 436 of SEQ ID NO: 1. However, Applicant's specification teaches at page 4, lines 19-21 that the nucleotide position -765 corresponds to nucleotide 436 of SEQ ID NO: 1. Papafili et al meets this limitation.

Papafili et al additionally teach wherein the nucleotide position -765 is associated with a G>C mutation, the genotype distribution was GG, GC and CC. Papafili teach the -765 G>C mutation is associated with a cardiovascular disease and with sensitivity to a non steroidal anti-inflammatory drugs (page 1633, page 1634, col. 2, lines 14-21, and page 1635, col. 1, third full paragraph).

Regarding claim 2, wherein the genomic DNA is extracted from cells of a subject derived from blood sample (page 1632, col. 2).

Regarding claim 3 and 4, Papifili et al teach wherein the cardiovascular pathology is coronary by-pass (see page 1632) which is inherently associated with ruptured atherosclerotic plaque.

Regarding claims 5 and 6, Papifili et al teach a method wherein the identification is carried out by endonuclease digestion with restriction enzymes (see page 1632, col. 2).

Regarding claim 7, Papifili et al teach wherein the method comprises extracting genomic DNA from a biological sample of a subject, amplifying by PCR with primers suitable for amplification of a DNA fragment comprising position -765, enzymatically digesting the amplified fragment with the restriction enzyme Aci I, electrophorectically separating the restriction mixture comprising the restriction fragments or of the

undigested amplified fragment and analyzing the restriction profile generated after visualization of DNA (see page 1632, col. 2). Therefore, Papifili et al meets the limitations of the claims recited above.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claim 1 is rejected under 35 U.S.C. 102(a) and/or 35 U.S.C. 102(e) as being anticipated by Thomann et al (20030082550, publication date May 1, 2003, effective filing date September 2000). Regarding claim 1, Thomann et al teach a method of identifying a nucleotide at position 436 of SEQ ID NO: 1 (see Figure 2A). Therefore, Thomann et al meet the limitation of the claim 1.

Conclusion

10. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/

Examiner, Art Unit 1637